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PATENT APPLICATION
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UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Marvin L. Vestal		
Application No.:	09/755,951	Art Unit:	1743
Filed:	January 4, 2001	Examiner:	Arlen Soderquist
For:	Mass Spectrometer System and Method for Matrix-Assisted Laser Desorption Measurements		

SECOND DECLARATION OF ROBERT S. BROWN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

I, Robert S. Brown, hereby declare as follows:

1. I am currently a tenured Professor of Chemistry, Department of Chemistry and Biochemistry, at Utah State University. I have served on the Chemistry and Biochemistry Department faculty since January of 1994. Prior to that I served as an Assistant Professor on the faculty of the Chemistry Department at Colorado State University. I hold a Ph.D. in Chemistry from the Virginia Polytechnic Institute and State University. As a research scientist, I began work in the field of mass spectrometry in 1983. In the past 20 years I have contributed to the development of the mass spectroscopy field in general and matrix assisted laser desorption/ionization (MALDI) mass spectrometers in particular. I have published numerous articles on mass spectroscopy, time-of-flight mass spectroscopy and laser desorption/ionization ion sources for use with mass spectrometers.

2. During my career, I have developed a number of time-of-flight mass spectrometers and mass spectrometry techniques. In particular, I have developed several laser desorption/ionization time-of-flight mass spectrometers and techniques for their use.

3. During my career, I have supervised and served as a thesis advisor to graduate students in doctoral programs at Utah State University and Colorado State University since at least 1987. In addition, I have taught numerous undergraduate and graduate courses in which part of the subject matter concerns mass spectrometry since at least 1987. Also, since 1983 I have regularly attended professional meetings in the field of mass spectrometry. I am therefore familiar with the spectrum of skill levels of workers in the field of mass spectrometry.

4. My experience and education, including a list of publications I have authored, are summarized in my *curriculum vitae*, a true and accurate copy of which is provided with this declaration.

5. Prior to the filing of the present patent application (U.S.S.N. 09/755,951), I was retained as a consultant to Applied Biosystems a Division of Applera Corp. and the successor to PerSeptive Biosystems (hereafter "Applied Biosystems"). I have been compensated for these services at my customary rate of $2,000.00 per day of consultation. It is my understanding that I continue to be retained as a consultant to Applied Biosystems at my customary rate for the present patent application. My compensation for these services is not contingent upon the issuance of the present patent application or outcome of this or any other action.

6. In preparing this declaration, I have reviewed the following documents:

- U.S. Patent No. 5,498,545 issued on March 12, 1996, to Vestal, and reissued as RE37,485 on December 25, 2001 to Vestal;
- A copy of U.S. Application No. 09/755,951 filed on January 4, 2001. ("the Vestal application");

- A copy of the currently pending claims in U.S. Application No. 09/755,951 as of December 5, 2002. ("the Vestal claims" or "the pending claims");
- U.S. Patent No. 5,288,644 issued on February 22, 1994 to Beavis et al. ("the Beavis patent");
- U.S. Patent No. 5,045,694 issued on September 3, 1991 to Beavis et al. ("the'694 patent");
- "An Automatic Analytical Laboratory for Mass-Spectrometric Isotopic-Dilution Analysis of Uranium and Plutonium in Fuel Solutions," Safegaurds Tech., Proc. Symp., 2, pages 165-176 (1970) by Wilhelmi et al. ("the Wilhelmi article");
- U.S. Patent No. 5,382,793 issued on January 17, 1995 to Weinberger et al. ("the Weinberger patent");
- "Automated Sample Transport System for Chromatography/ Secondary Ion Mass Spectrometry" Rev. Sci. Instrum. 60 (6), pages 1071-1074 (1989) by Duffin et al. ("the Duffin article");
- U.S. Patent No. 5,037,611 issued on August 6, 1991 to Ledford ("the Ledford patent");
- "A Direct Insertion Sample Handling System for Mass Spectrometers" Int. J. Mass Spectrom. Ion Phys., 3, pages 159-160 (1969) by Bakker and Williams ("the Bakker article");
- The Office Action mailed from the U.S. Patent and Trademark Office on January 24, 2003, for U.S. Application No. 09/755,951;
- The Office Action mailed from the U.S. Patent and Trademark Office on September 8, 2003, for U.S. Application No. 09/755,951 ("the Office Action");
- "Experiments with an Automatic mass Spectrometer in the Isotopic Analysis of Nuclear Fuels" Advances in Mass Spectrometry, 7B, pages 1052-1061 (1978) by Koch et al. ("the Koch article");
- U.S. Patent No. 4,911,815 issued on March 27, 1990 to Kamei et al.;
- "Improvements in the Application of a Tandem Van De Graff Accelerator for Ultrasensitive Mass Spectrometry" Argonne National Lab., Physics Div. ANL/PHY-81-1, pages 87-99 (1981) by Suter et al.;
- "Characterization and Improvement of Gaseous Contamination Levels in a Multi-Chamber Etch Tool" 39th Proceedings-Institute of Environmental Sciences, Vol. 1, pages 124-127 (1993); and

- The Declaration of Robert S. Brown Under 37 C.F.R. § 1.132 (the "First Declaration") filed on July 24, 2003, with U.S. Patent and Trademark Office, for U.S. Application No. 09/755,951, together with a Reply to the Office Action mailed from the U.S. Patent and Trademark Office on January 24, 2003, for U.S. Application No. 09/755,951.

7. My statements in this declaration are based upon my knowledge of the mass spectrometry field, over 20 years of experience with the field and practitioners, and review of the documents listed in paragraph 6. Against this backdrop, I make the following statements of fact and observations.

8. I have been asked to evaluate the references cited in the Office Action. I will refer to the references cited in the Office Action collectively as the cited references. I have also been asked to evaluate the Vestal application and pending claims. In my evaluation, I have been asked to consider the state of the mass spectrometry field as it existed on July 21, 1994. It is my understanding that the present application claims the benefit of July 21, 1994, as its effective filing date.

9. I have considered and been asked to evaluate to what extent, if any, the cited references disclose a system for obtaining mass data having one or more of the following features:

(1) a system having a sample support transfer mechanism adapted to:

disassociate a first sample support from a sample receiving stage, transport the first sample support from an ion source chamber through an output port to a vacuum lock chamber and to associate the first sample support with a sample support holder; and

disassociate a second sample support from the sample support holder, transport the second sample support from the vacuum lock chamber through the output port to the ion source chamber and to associate the second sample support with the sample receiving stage;

(2) the system of (1) above including a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane;

(3) the system of (1) or (2) above where the system is configured so the vacuum lock chamber and the ion source chamber are in fluid communication and under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports;

(4) the system of (1), (2), or (3) above where the sample support holder is disposed in the vacuum lock chamber or sample storage chamber;

(5) the system of (1), (2) or (3) above where a sample storage chamber is connected to the vacuum lock chamber; or

(6) the system of (5) above where the sample support holder is disposed in the sample storage chamber.

In evaluating whether the above systems of (1)-(6) are disclosed in the cited references, I have considered the vacuum lock chamber to be connected with the ion source chamber. I have also evaluated what was described or suggested in the cited references, both separately and together, to one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the systems above to obtain mass data. As a shorthand, I will refer to the support transfer mechanism of (1) above as the "Vestal transfer mechanism".

10. I have also considered and been asked to evaluate to what extent, if any, the cited references disclose a method for obtaining mass data having at least the following steps:

(1) moving a first sample support associated with a sample receiving stage within an ion source chamber in an x direction and in a y direction perpendicular to the x direction;

striking with a laser pulse a desired number of a plurality of samples on the first sample support within the ion source chamber to desorb and ionize sample molecules;

disassociating the first sample support from the sample receiving stage;

transporting the first sample support form the ion source chamber to a vacuum lock chamber;

associating the first sample support with a sample support holder;

disassociating a second sample support from the sample support holder;

transporting the second sample support from the vacuum lock chamber to the ion source chamber;

associating the second sample support with the sample receiving stage;

moving the second sample support associated with the sample receiving stage within the ion source chamber in an x direction, and in a y direction perpendicular to the x direction; and

striking with a laser pulse a desired number of a plurality of samples on the second sample support within the ion source chamber to desorb and ionize sample molecules; or

(2) the method for obtaining mass data including the steps of (1) above in this paragraph where the vacuum lock chamber and ion source chamber are in fluid communication and are maintained under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports.

I have also evaluated what was described or suggested in the cited references, both separately and together, to one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994, regarding the use of the steps above to obtain mass data.

11. I have been asked based on my knowledge (which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994) whether the systems for obtaining mass data as described in the Vestal application and Vestal claims 75-87, 90-91, 95 and 97, when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 75-87, 90-

91, 95 and 97, as a whole was recommended by or apparent to one of ordinary skill in the art in the mass spectrometry field as it existed on July 21, 1994.

12. I have also been asked based on my knowledge (which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994) whether the methods for obtaining mass data as described in the Vestal application and Vestal claims 92-94 when viewed as a whole, was known to the mass spectrometry field, as it existed on July 21, 1994, or that practicing one or more of Vestal claims 92-94 as a whole was recommended by or apparent to one of ordinary skill in the art in the mass spectrometry field as it existed on July 21, 1994.

13. It is my understanding that a person of ordinary skill in the art is one who thinks along the line of conventional wisdom in the art. A person of ordinary skill in the art is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights. Based on my over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and practitioners of all skill levels in this field as it existed on July 21, 1994, one of ordinary skill in the field of mass spectrometry as it existed on July 21, 1994 would have possessed an education in Chemistry or Physics at a Masters degree level and been competent in the use of mass spectrometry instrumentation. I understand that one of ordinary skill in the art is a "hypothetical person" who does not necessarily exist.

14. I have again reviewed the Vestal application. In view of paragraph 13 above, I maintain and reiterate my reading and view of the Vestal application expressed in paragraphs 13, 14 and 15 of my First Declaration. It is my view that one of ordinary skill in the field of mass spectrometry, upon reading the Vestal application, would understand that the Vestal application describes systems where a sample support holder can be placed in the vacuum lock chamber even for those systems that do not have a sample storage chamber. In my view and

based on my experience with practitioners in the field, upon reading the Vestal application one of ordinary skill in the field of mass spectrometry would also understand that the Vestal application describes structures and methods that permit the vacuum lock chamber and the ion source chamber to be in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports. It is my view that one of ordinary skill in the field of mass spectrometry would understand that such systems are included in the description at column 6, line 50, to column 9, line 51, of the Vestal application. It is also my view that one of ordinary skill in the field of mass spectrometry would understand that methods for obtaining mass data using a sample support holder in the vacuum lock chamber without a sample storage chamber, and methods where the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of first and second sample supports, are both described by the Vestal application.

15. I understand the Vestal application to claim and describe various systems that include a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. I understand the Vestal application to describe and claim in claims 75-87, and 95 a system that includes a mechanism to move the sample receiving stage in an x direction and in a y direction perpendicular to the x direction, where the x direction and the y direction lie substantially in the same plane. I also understand the Vestal application to describe and claim in claims 90-91 and 97 a system that includes a sample storage chamber connected to the vacuum lock chamber. I further understand the Vestal application to describe and claim in claims 95 and 97 a system that includes structures configured so that the vacuum lock chamber and the ion source chamber are in fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of the first and second sample supports. In addition, I understand the Vestal application to describe the use of a sample

support holder capable of holding multiple sample supports in the vacuum lock chamber or a sample storage chamber. As a shorthand, I will refer to the various systems laid out in Vestal claims 75-87, 90-91, 95, and 97 collectively as the "Vestal systems."

16. I understand the Vestal application to claim methods for obtaining mass data. I understand from the Vestal application that the methods laid out in claims 92-94 involve using at least the steps of (1) in paragraph 10. I further understand from the Vestal application that the method laid out in claim 93 involves having the vacuum lock chamber and ion source chamber in fluid communication while also under a vacuum controlled environment during the dissociating, transporting, and associating of the first and second sample supports. As a shorthand term, I will refer to the methods laid out in Vestal claims 92-94 collectively as the "Vestal methods."

17. I understand the Beavis patent to describe a system where a sample disk is attached directly to the shaft of a stepper motor and the sample disk is then somehow loaded into the ion source through a vacuum lock. However, I can find no description in the Beavis patent that describes how one could either attach or detach the sample disk of Beavis to the stepper motor under a vacuum controlled environment. It is my view that Beavis indicates that attachment and detachment do not occur under a vacuum controlled environment at column 4, lines 65-67, when he instructs that, "any gas introduced in this procedure [the insertion of a disk into the ion source] must be removed prior to measuring the mass spectrum," and at column 5, lines 25-29, where Beavis indicates that pumpdown is required after inserting a new sample disk, "less than five minutes of each two hour period is required for loading and pumpdown." Based on my experience, the Beavis patent provides no description or suggestion to one of ordinary skill in the field of mass spectrometry of how to load sample disks while under a vacuum controlled environment onto the stepper motor or onto any other device that can move the sample disk. Based on my experience, the Beavis patent also does not provide any guidance to one of

ordinary skill in the field on how to modify his system to load sample disks under a vacuum controlled environment.

18. I can find no description in the Beavis patent that describes the use of a sample support holder in either a vacuum lock chamber connected with the ion source chamber or a sample storage chamber connected to the vacuum lock chamber. In addition, I can find no description in the Beavis patent that describes a transport mechanism configured to transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage as discussed in paragraph 9 above. Based on my experience, the Beavis patent also does not provide any guidance to one of ordinary skill in the field on how to modify his system to include a sample support holder or a transport mechanism as discussed in paragraph 9 above.

19. I have also reviewed the '694 patent which I understand to be the patent which issued from U.S. Patent Application Serial No. 07/413,321 referenced at column 5, lines 5-10 in the Beavis patent. I have been asked to review the '694 patent to place in context the phrase "even if the samples were manually loaded, as disclosed in [sic] copending U.S. Pat. application Ser. No. 07/413,321" appearing at column 5, lines 5-10, in the Beavis patent. The '694 patent does not describe any structure for rotation or x-y translation of the sample probe once inside the ion source. The '694 patent does refer to sample loading, in the same fashion it is referred to in the Beavis patent, at column 6, lines 29-31 which reads, "With a typical sample loading of 0.1-20 p mol of analyte on the probe tip (3 mm^2) good signals were observed." Based on my experience and the lack of any description in the '694 patent of specific probe movement once inside the ion source, and the use of the term sample loading to refer to spotting of the sample on a probe tip, I understand and one of ordinary skill in the field of mass spectrometry would understand the text in the Beavis patent on manual and automatic sample loading to be referring to the spotting of samples onto the sample disk and not the loading of a sample disk onto a stepper

motor. In addition, I understand and one of ordinary skill in the field of mass spectrometry would understand the text at column 4, lines 4-9, in the '694 patent ("The probe **10** is manually inserted and may be manually removed from the round bore **12** of the metal wall **13** of the spectrometer"), to not be the part of the '694 patent the Beavis patent is referring to at column 5, lines 5-10 because this part of the '694 patent only concerns the probe and the Beavis patent makes clear that sample loading refers to the loading of sample onto the sample disk.

20. I have again reviewed the Beavis patent with respect to what one of ordinary skill in the field of mass spectrometry would understand the text in the Beavis patent to suggest. Particularly, I have again reviewed the paragraph in the Beavis bridging columns 4 and 5, and lines 5-10 at column 5 in the Beavis patent. In my view, one of ordinary skill in the field of mass spectrometry would not understand the Beavis patent to suggest automation of sample disk insertion into or transport of the sample disk within a mass spectrometer, for many reasons. First the paragraph bridging columns 4-5 refers to a singular disk, not multiple disks. The sentences at lines 5-10 refer to sample loading, making no mention of sample disk insertion. Based on my experience, one could not reasonably read into lines 5-10 a reference to sample disk insertion and one of ordinary skill in the field would not read these lines as referring to sample disk insertion. Based on my experience, one of ordinary skill in the field would read the reference in lines 5-10 to sample loading to refer to the meaning and context they are given throughout the Beavis patent. I and one of ordinary skill in the field would understand that the Beavis patent clearly shows that sample loading is the loading, shown to be spotting, of sample onto a sample disk. I and one of ordinary skill in the field would understand that the Beavis patent's Figure 1 clearly illustrates one such sample loading approach which he calls, "a suitable automated DNA sample preparation and loading technique" and that this is what the Beavis patent refers to when in column 5, lines 14-17, he claims "The technique of the present invention does not...require the full time attention of a dedicated, trained operator to prepare and load the samples." I and one of ordinary skill in the field would understand that the time savings the Beavis patent is discussing in column 5, lines 5-10, and the bridging paragraph of

columns 4-5, are those given by using mass spectrometry instead of gel electrophoresis to analyze a sample and (with Figure 1 and the Beavis patent's claim in column 5, lines 14-17, that the full time attention of a dedicated, trained operator to prepare and load the samples is not required) automated preparation of samples and automated loading onto a sample disk. Thus, I do not understand, and in my view one of ordinary skill in the field of mass spectrometry would not understand the Beavis patent to suggest automation of sample disk insertion into a mass spectrometer or suggest the automation of the transport of the sample disk within a mass spectrometer.

21. I understand the Wilhelmi article to be concerned with mass spectrometric measurements of uranium and plutonium in nuclear fuel samples placed as solutions onto evaporator filaments (which I subsequently refer to as sample filaments) and dried prior to mass spectrometry analysis. Based on an examination of Figure 3 and its description, Wilhelmi appears to illustrate a system that uses several mechanisms to move a cassette containing beads of nuclear material where each bead is deposited on heating filament. The Wilhelmi system appears to use a mechanism to place the cassette into a preheating chamber and a mechanism is presumably used to move the heated cassette to a lock chamber. A separate pushrod mechanism is used to push a sample filament (referred to as a "bead" in the article) into the ion source where it is vaporized by heating the filament, which appears to also be referred to as an evaporation filament. The vapor that results is then ionized by electrons emitted by the ionization filament in the ion source (electron impact ionization).

22. However, it is my view that the Wilhelmi article does not describe or suggest that the sample filament (or bead) is ever detached from the end of the pushrod (also referred to as a "pinch rod" in the text) during mass spectrometric analysis. It is my view that the sample filament probably does not leave the end of the pushrod based on several parts of the text description. First, the Wilhelmi article does not mention any separate stage to receive a sample filament. Second, the Wilhelmi article states at page 172 that "as soon as the bead is introduced

into the ion source the measurement starts" indicating in my view that the pushrod does not detach from the bead (sample filament) during this step. Third, because there is only one sample filament, sample bead, introduced at a time into the ion source and the sample is vaporized by heating a sample filament, there appears to be no reason to associate the sample filament with a separate stage. Based on my experience, the Wilhelmi article provides no description or suggestion to one of ordinary skill in the field of mass spectrometry to associate or disassociate a sample support with a receiving stage, or any guidance to one of ordinary skill in the field on how to modify his mechanism to either associate or disassociate a sample support with a receiving stage.

23. Making use of the drawing item numbers in the Weinberger patent, I understand the Weinberger patent to describe a system where a shaft (154) is used to pick up a probe tip (30) from a sample ring (152), the probe tip is then pushed into an ion optics region (32) but the probe remains attached to the shaft during mass spectrometric analysis because it is used to rotate the probe tip which contains the sample for analysis. The shaft (154) has o-ring seals (shown in Figure 6), one of which vacuum isolates the ion optics region (32) from the sample chamber (28) containing the sample ring (152) once the ball valve lock (172) is opened and a probe tip has been fully inserted. This o-ring seal prevents fluid communication between the sample chamber (28) and ion optics region (32) by apparently sealing against the ion optic entrance channel (170) when the ball valve lock (172) is opened and the probe tip is fully inserted. The Weinberger patent's structure of a shaft in a channel also prevents x-y translation of the probe during mass spectrometric analysis.

24. It is my view that the Weinberger patent does not describe or suggest a structure that enables a sample support to be dissociated from a transport mechanism and associated with a receiving stage. It is also my view that the structures described and suggested by the Weinberger patent are incompatible with the use of a receiving stage that provides x-y translation because they technically cannot be made to work with such a receiving stage because

modification of the shaft of the Weinberger patent for combination with Beavis to execute x-y translation, would render the mechanism of the Weinberger patent inoperable for its intended purpose. More specifically, the mechanism of the Weinberger patent includes the shaft (154) with o-ring seals and an entrance channel arrangement which is meant to operate so the o-rings on the shaft seal against the ion optic entrance channel (170) when the probe tip is fully inserted and yet allow the shaft to rotate the probe tip while vacuum isolating the ion optics region (32) from the sample chamber (28). Using the technical teachings of the Weinberger patent, modification of the Weinberger patent shaft channel assembly so the shaft could execute x-y translation would disrupt the seal provide by the shaft o-ring which isolates the ion optics region, and this would render the Weinberger patent mechanism inoperable for its intended purpose. Based on my experience, the Weinberger patent does not provide any guidance to one of ordinary skill in the field on how to modify his mechanism to either: (a) associate or disassociate a sample support with a receiving stage; (b) associate or disassociate a sample support with a receiving stage that provides x-y translation; or (c) permit a vacuum lock chamber and an ion source chamber to be in continuous fluid communication while also under a vacuum controlled environment during disassociation, transportation and association of sample supports; as any of these are set forth in Vestal claims 75-87, 90-94, 95, and 97 or in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

25. I understand the Duffin article to describe a piezoelectric actuated x-y translation stage. However, the Duffin article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber or associate and dissociate sample supports with either a sample support holder or sample receiving stage other than via a manual procedure which requires venting to atmosphere the entire instrument. In my view, the Duffin article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock

chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

26. It is my understanding that the Office Action makes reference to the Ledford patent for its use of indicia to provide indexing and sample information. In my view the Ledford patent however does not describe or suggest a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

27. I understand the Bakker article to illustrate a system with a swing butterfly valve but the Bakker article does not describe or suggest the use of any mechanism that can either transport a sample support to and from an ion source chamber to a vacuum lock chamber and associate and dissociate sample supports with a either a sample support holder or sample receiving stage. While swing butterfly valves and other vacuum isolation methods such as gate valves and ball valves would have been known to practitioners of ordinary skill in the field of mass spectrometry, the Bakker article also does not provide any suggestion or description that would have provided guidance to the ordinary practitioner in the field of mass spectrometry as of July 21, 1994, on how to make or use a mechanism that could transport sample supports to and from an ion source chamber through an output port to a vacuum lock chamber and to associate and dissociate sample supports with a sample support holder and sample receiving stage in a manner equivalent to those described in (1)-(6) in paragraph 9 above.

28. Based on my experience, there is no equivalent operator hands-on activity to a mechanism equivalent to those described in (3)-(6) in paragraph 9; or in (2) in paragraph 10 above because a human cannot associate, transport or disassociate a sample support with a receiving stage as described in (3)-(6) in paragraph 9 or in (2) in paragraph 10 while the vacuum lock chamber and the ion source chamber are in continuous fluid communication and under a

vacuum controlled environment during disassociation, transportation and association of the sample supports without exposing the operator to the detrimental effects of vacuum.

29. It is my view that while various versions of sample supports, sample holders, sample receiving stages, and mechanisms to hold and move sample supports were known to the mass spectrometry field, as of July 21, 1994, the steps necessary to modify such existing components and produce an instrument in keeping with one or more of the Vestal systems, were not known, and would not have been apparent to one of ordinary skill in the mass spectrometry field as of July 21, 1994, without the disclosure provided by the Vestal application. It is my view that the likelihood that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would have been able to modify and combine the cited references to produce one or more of the Vestal systems was remote. Thus, it is my view (based on my experience, which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994), that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would not have had a reasonable expectation of successfully combining the cited references to produce one or more of the Vestal systems. Based on my experience, any expectation of success by one of ordinary skill in the field would have been unreasonable because it would have required extensive experimentation to determine how to modify and then modify and combine existing components to produce a system in keeping with one or more of the Vestal systems. First, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a transfer mechanism such as the Vestal transfer mechanism. Second, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no guidance on how such existing components could be modified and combined to produce one or more of the Vestal systems.

30. Based on my experience it is my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no working examples of a method for obtaining mass data in a manner equivalent to those of one or more of the Vestal methods. Based on my experience it is also my view that, absent the Vestal application, the cited references and to my knowledge the mass spectrometry field as of July 21, 1994, provided no description of an instrument or guidance on how to combine existing structures to produce a working instrument that could be used to obtain mass data in a manner equivalent to that of one or more of the Vestal methods. Thus, it is my view (based on my experience, which includes over 20 years of experience in the mass spectrometry field, and contemporaneous knowledge of both the mass spectrometry field and those of ordinary skill in this field as it existed on July 21, 1994), that one of ordinary skill in the field of mass spectrometry as of July 21, 1994, would not have had a reasonable expectation of successfully combining the cited references to practice one or more of the Vestal methods.

31. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued in reliance thereon.

Date: March 5, 2004

Robert S. Brown

Robert S. Brown, Ph.D.